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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FISHER, ABIGAIL L	

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1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,939	ANDERBERG ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *October 20 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-11,15,19-24,27,28 and 32* is/are pending in the application.

4a) Of the above claim(s) *4,6,9,10,15,21-24,27 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 11, 19-20, and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/05, 12/30/05, 1/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Response to Election/Restriction filed on 10/20/08 is acknowledged. Claims 7-8, 12-14, 16-18, 25-26, and 29-31 were/stand cancelled. Claims 1-6, 9-11, 15, 19-24, 27-28 and 32 are pending.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 1/12/05, 12/30/05, 1/6/06 were considered by the examiner.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on October 20 2008 is acknowledged. The traversal is on the ground(s) that that the special technical feature that is common in all groups is an IBAT inhibitor and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum, and or the colon. This is not found persuasive because the prior art cited in order to show that the common technical feature was known (US Patent No. 6387924 to Lee et al.) teaches that the compounds of the invention are delivered to the ileum of a mammal (column 281, lines 15-16). Since one particular form of the compound is that of a calcium salt, the composition of Lee et al. comprise an IBAT inhibitor (benzothiepine), a calcium salt and is delivered to the ileum.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 9-11, 15, 19-24, 27-28 and 32 are pending in the application. Claims 4, 6, 9-10, 15, 21-24, 27 and 32 are withdrawn from further consideration pursuant to 37

CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 20 2008. Accordingly, claims 1-3, 5, 11, 19-20 and 28 are being examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 11, 19-20 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The specification, while being enabling for specific IBAT inhibitors and their pharmaceutically acceptable salts, does not reasonably provide enablement for solvates or solvates of the pharmaceutically acceptable salts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should

proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Formal, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, relative skill level, and breadth of the claims

The instant invention is directed to a combination which comprises and IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt and a metal salt.

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The complex nature of the claims is greatly exacerbated by the breath of the claims. The claims encompass any solvate or solvate of a salt.

The relative skill of those in the art is high, that of an MD or PHD.

The state and predictability of the art

As illustrative of the state of the art, the examiner cites Grant et al. Grant et al. (Advanced Drug Delivery Reviews, 2001) indicates that predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice is both complex and difficult. All compounds respond differently to possible formation of hydrates. Therefore Grant et al. indicates that generalizations cannot be made for a series of compounds and their respective hydrates (page 19, section 3.4).

The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for how to form a solvate or solvate of a salt. Due to the vastness of compounds classified as IBAT inhibitors, one of ordinary skill would undergo undue experimentation in deducing which compounds can actually form solvates or solvates of salts as well as which solvent can actually be utilized to form such the solvate.

Thus, in the absence of working examples there is no showing that the instant compounds will form solvates or solvate of salts. Since it is clear that merely bringing the compound into contact with water does not result in a hydrate/solvate additional direction or guidance is needed to make them and the specification has no such

direction or guidance.

The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed compounds can form solvates and solvates of the salts of the compounds as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 1-3, 5, 11, 19-20 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claim(s) 1-3, 5, 11, 19-20 and 28 is(are) directed to encompass prodrugs, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these prodrugs

meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim. **Note: MPEP 2163.**

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, (Fed. Cir. 1991), makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004), further supports this by stating that:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed prodrugs regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Circ. 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, (Fed. Cir. 1991). In Fiddes v. Baird, 30 USPQ2d 1481, 1483, (Bd. Pat. App. & Int. 1993), claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 (Fed. Cir. 1997) held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.

> 1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Furthermore, to the extent that a functional description can meet the requirement for an adequate written description, it can do so only in accordance with PTO guidelines stating that the requirement can be met by disclosing "sufficiently detailed, relevant identifying characteristics," including "functional characteristics when coupled with a known or disclosed correlation between function and structure." Univ. of Rochester v. G.D. Searle, 68 USPQ2d 1424, 1432 (DC WNY 2003).

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 11, 19-20 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Starke et al. (WO 02/32428, "Starke et al. '428", cited on PTO Form 1449) in view of Starke et al. (WO 02/50051, "Starke et al. '051", cited on PTO Form 1449) and Friend et al. (US Patent No. 5811388).

Applicant Claims

Applicant claims a combination comprising and IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate. A specific IBAT inhibitor claimed is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine. A further limitation is that the composition additionally comprises an HMG CoA reductase inhibitor. A further limitation is that the combination is in association with a pharmaceutically acceptable diluent or carrier.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Starke et al. '428 is directed to a pharmaceutical formulation comprising an IBAT inhibitor, an HMG Co-A reductase inhibitor and a therapeutically acceptable carrier which is designed to deliver the IBAT inhibitor into the ileum (abstract and page 1, lines 3-11). IBAT inhibitors taught include 1,4-benzothiazepines and 1-5, benzothiazepines (page 4, lines 28-31). Preferred compounds include those with an oxidized sulphur group, particularly a sulphone in the 7 member ring and the presence of an amine in the 7 member ring (page 5, lines 1-3). HMG Co-A reductase inhibitors are taught as being well known in the art and include fluvastatin, lovastatin, pravastatin, simvastatin, etc. (page 5, lines 6-12). It is taught that the combination of HMG CoA reductase inhibitor will have an additive effect in combination with an IBAT inhibitor on lipid lowering (column 7, lines 13-14). The core material containing the IBAT inhibitor can be formulated as monolithic tablets, capsules, granules, pellets, etc. The IBAT inhibitor

can be mixed with further components such as binders, surfactants, lubricants, etc. (column 8, lines 10-20).

Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)

Starke et al. '428 do not teach that the IBAT inhibitor is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine. However, this deficiency is cured by Starke et al. '051.

Starke et al. '051 teach the synthesis of IBAT inhibitors. It is taught that the IBAT inhibitors of the invention can be administered simultaneously, sequentially, or separate administration with an effective amount of an HMG Co-A reductase inhibitor (page 45, lines 7-20). The compositions are taught as being in association with a pharmaceutically acceptable diluent or carrier (page 45, lines 20-30). One specific IBAT inhibitor taught is 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (example 43).

Starke et al. '428 do not teach that the formulation comprises calcium phosphate. However, this deficiency is cured by Friend et al.

Friend et al. is directed to the delivery of drugs to the lower GI tract. It is taught that one or more excipients may be included in drug formulation to impart satisfactory processing and compression characteristics and to give additional desirable physical characteristics to the tablets. Mostly the excipients aid in the delayed release of the

drug form the composition to achieve regional delivery to the lower GI track (column 11, lines 22-30). It is taught that excipients that are used fulfill several roles, i.e. an excipient that acts as binder to not only increase the hardness but also aid in the delayed release/regional delivery include non-gas forming mineral salts (columns 11-12, lines 60-67 and 1-4). One useful mineral salt is calcium phosphate (column 12, lines 15-16).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Starke et al. '428, Starke et al. '051 and Friend et al. and utilize 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine as the IBAT inhibitor. One of ordinary skill in the art would have been motivated to utilize 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine as Starke et al. '428 teach that the IBAT inhibitors that can be incorporated are preferably 1,5-benzothiazepines with a sulphone and amine in the 7 member ring and 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)-1'-{N'-(carboxymethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine taught by Starke et al. '051 is an IBAT inhibitor that is a 1,5-benzothiazepine with a sulphone and an amine in the 7 member ring.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Starke et al. '428, Starke et al. '051 and

Friend et al. and utilize calcium phosphate in the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to utilize calcium phosphate as Starke et al. '428 teach that the IBAT inhibitor can be mixed with further components such as binders, surfactants, lubricants, etc. and Friend et al. teach that calcium phosphate is an specific binder that not only increases the hardness of the composition but aids in the delayed release and regional delivery profile. Since Starke et al. '428 teach it is desirable to have the IBAT inhibitor released in the ileum, one of ordinary skill in the art would have been motivated to add excipients that aid in the regional delivery profile desired as taught by Friend et al.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 7192945 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '945 claims a pharmaceutical compositing comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier. A particular species of formula I is the same as the instantly elected species.

Patent '945 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

Friend et al. is directed to the delivery of drugs to the lower GI tract. It is taught that one or more excipients may be included in drug formulation to impart satisfactory processing and compression characteristics and to give additional desirable physical characteristics to the tablets. Mostly the excipients aid in the delayed release of the drug form the composition to achieve regional delivery to the lower GI track (column 11,

lines 22-30). It is taught that excipients that are used that fulfill several roles, i.e. an excipient that acts as binder to not only increase the hardness but also aid in the delayed release/regional delivery include non-gas forming mineral salts (columns 11-12, lines 60-67 and 1-4). One useful mineral salt is calcium phosphate (column 12, lines 15-16).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '945 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-18 of U.S. Patent No. 7192945 in view of Friend et al. and Starke et al. (WO 02/32428).

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '945 are set forth above.

Patent '945 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

Starke et al. teach that IBAT inhibitors are designed to be delivered into the ileum (abstract and page 1, lines 3-11). It is taught that the combination of HMG CoA reductase inhibitor will have an additive effect in combination with an IBAT inhibitor on lipid lowering (column 7, lines 13-14). HMG Co-A reductase inhibitors are taught as being well known in the art and include fluvastatin, lovastatin, pravastatin, simvastatin, etc. (page 5, lines 6-12).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '945, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of

U.S. Patent No. 6906058 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '058 claims a pharmaceutical composition comprising compounds of Va, Vb, VIIa and VIIb or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of Va, Vb, VIIa and VIIb are 1,5-benzodiazapines and are IBAT inhibitors.

Patent '058 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '058 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6906058 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '058 are set forth above.

Patent '058 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '058, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of U.S. Patent No. 7192947 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '947 claims a pharmaceutical composition comprising compounds of formula I or I' or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I or I' are 1,5-benzodiazapines and are IBAT inhibitors.

Patent '947 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '947 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8 of U.S. Patent No. 7192947 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '947are set forth above.

Patent '947 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '947, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated

to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 1-3, 5 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7192946 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '946 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are 1,5-benzodiazapines and are IBAT inhibitors.

Patent '946 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '946 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art

would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7192946 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '946 are set forth above.

Patent '946 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '946, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that

the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 1-3 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7132416 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '416 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are 1, 2, 5-benzodiazapines and are IBAT inhibitors.

Patent '416 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '416 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 13 of U.S. Patent No. 7132416 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '416 are set forth above.

Patent '416 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '416, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Note: If the elected species is found to be allowable, the obvious type double patenting rejection will be expanded to include claims 3 or 6.

Claims 1-3 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12 of U.S. Patent No. 7238684 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '684 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are 1, 2, 5-benzodiazapines and are IBAT inhibitors.

Patent '684 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '684 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 and 12 of U.S. Patent No. 7238684 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '684 are set forth above.

Patent '684 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '684, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Note: If the elected species is found to be allowable, the obvious type double patenting rejection will be expanded to include claims 3 or 6.

Claims 1-3, 11, 19-20 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 13-15 of U.S. Patent No. 7226943 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '943 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. Additionally claimed is a pharmaceutical composition comprising the compounds of formula I and a HMG Co-A reductase inhibitor. The compound is a benzothiepine and a IBAT inhibitor.

Patent '943 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '943 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Note: If the elected species is found to be allowable, the obvious type double patenting rejection will be expanded to include claims 3 or 6.

Claims 1-3 and 11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11 of U.S. Patent No. 7125864 in view of Friend et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims an IBAT inhibitor and a metal salt. A specific metal salt claimed is calcium phosphate.

Patent '864 claims a pharmaceutical composition comprising compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent. The compounds of formula I are IBAT inhibitors.

Patent '864 does not claim the addition of a metal salt. However, this deficiency is cured by Friend et al.

The teachings of Friend et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '864 and Friend et al. and add a conventional excipient such as calcium phosphate to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add conventional excipients such as calcium phosphate

in order to impart satisfactory processing and compression characteristics of the formulation as well as to manipulate the release profile of the pharmaceutical preparation as taught by Friend et al.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Claims 19-20 and 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11 of U.S. Patent No. 7125864 in view of Friend et al. and Starke et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims overlap in scope.

The instant application claims further addition of an HMG Co-A reductase inhibitor in combination with an IBAT inhibitor.

The teachings of Patent '864 are set forth above.

Patent '864 does not claim the addition of a HMG Co-A reductase inhibitor. However, this deficiency is cured by Starke et al.

The teachings of Starke et al. are set forth above.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Patent '864, Friend et al., and Starke et al. and add HMG CoA reductase inhibitors to the pharmaceutical formulation. One of ordinary skill in the art would have been motivated to add HMG CoA reductase inhibitors because Starke et al. teach that the combination of HMG CoA reductase inhibitors and IBAT inhibitors have an additive

effect on lipid lowering. Therefore, when desiring a pharmaceutical formulation that will be utilized to lower lipid levels one of ordinary skill in the art would have been motivated to formulate a pharmaceutical formulation comprising both an IBAT inhibitor and HMG CoA reductase inhibitor.

Therefore, the scopes of the patent claims and the instant application overlap and thus they are obvious variants of one another.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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